DEPARTMENT OF HEALTH & HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

PHILADELPHIA DISTRICT

900 U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19106

Telephone: 215-597-4390

WARNING LETTER

May 31, 2000

00-PHI-16

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

A. Bruce Heck, Chief Executive Officer
Accupac, Inc.
1501 Industrial Boulevard
Mainland. PA 19451-0200

Dear Mr. Heck:

From March 21 through April 13, 2000 Philadelphia District personnel Colleen M. Damon and Michael Gurbarg conducted an inspection of your manufacturing facility located at 1501 Industrial Boulevard. Mainland, PA. These individuals documented numerous deviations from Current Good Manufacturing Practice (cGMP) regulations for finished pharmaceuticals specified in *Title 21 Code of Federal Regulations*, Parts 210 and 211. The following deviations cause the drug product [redacted] a liquid analgesic/decongestant medication that you manufacture for the [redacted] Company, to be adulterated within the meaning of Section 501(a)(2)(B) of the *Federal Food, Drug and Cosmetic Act* (the Act):

- Laboratory controls have not established that the test method for assay of [redacted] content of [redacted] is scientifically sound to assure that this product conforms to specifications of strength, quality and purity [21 CFR 211.160(b)].

  a) The method, as performed, fails to separate out the [redacted] component from other components in the product which precludes accurate quantitation of this ingredient.

  b) The suitability of the testing method was not verified under actual conditions of use.

  c) The calculation for assay fails to include a correction factor for the actual purity of the reference standard.

- Cleaning procedures for process equipment used interchangeably to manufacture pharmaceuticals, including [redacted] cosmetics, and invitro diagnostic solution. lack sufficient detail to assure contamination will not occur that could alter the safety. quality or purity of pharmaceutical products. [21 CFR 211.67].

  a) Cleaning procedures identify multiple approved cleaning/sanitizing chemicals but fail, in most cases, to identify which chemicals are to be used for each product.

b) There is no provision to document what cleaning chemicals are actually used.

c) The SOP for Sanitizing mixing vessels, storage tanks and phase tanks (SP#MF0017) was modified by a hand-written entry to include "[redacted]" as an approved cleaning detergent for this equipment. The suitability of this household detergent for use in cleaning drug contact surfaces has not been established.

d) The scientific basis for evaluating equipment cleanliness by means of a [redacted] measure of the rinse solution has not been established. Specifications for [redacted] and for [redacted] swab verification of equipment cleanliness have not been correlated to specific contaminants that may be present.

We have reviewed the May 12, 2000 letter from Robert S. Nase, Vice President Quality Assurance and Regulatory Affairs, responding to the Inspectional Observations, form FDA 483, presented to you April 13, 2000. We find this response does not address significant underlying cGMP issues.

For example, regarding the SOP that had been modified by hand to include "[redacted]" as an approved detergent for cleaning mixing vessels and storage tanks, the response letter advises that you will formally update the list of approved chemicals in the SOP and provide training sessions on revising cGMP documents. This response, however, fails to address other significant concerns such as whether "[redacted]", a *general household detergent,* is an acceptable product for use on direct drug contact surfaces and how you have assured that any residual carryover would be safe and would not be reactive with drug products formulated in these vessels.

Also. the response letter refers to cleaning validation data for [redacted] We would like to point out that cleaning validation must evaluate *specific* cleaning procedures that are capable of removing designated residues, including worse case scenarios. It is not adequate to swab equipment prior to use and promote this as cleaning validation.

The inadequacies in your equipment cleaning program are especially serious since your firm operates as a contract manufacturer that processes a variety of chemicals not intended for ingestion by humans, for example eye make-up remover, liquid make-up, invitro diagnostic solution. etc. Since your pharmaceutical clients would not have knowledge of specific chemicals processed in the same equipment, such contaminants could easily go undetected in product release testing.

It is critical. therefore, that sampling and testing methodology which you use to verify equipment cleanliness be capable of detecting specific residues that may reasonably be present from the products themselves or from chemicals used in cleaning operations. Determination of acceptable limits must likewise be contaminant-specific where potentially toxic residues may be present. Also. analytical methods for determining these limits must be validated.

A case in point is the recent contamination of saline nasal spray that you manufactured. Your client recalled this product from the market after complaints of discoloration and precipitation. Your investigation report states that retention samples of the bulk solution showed no evidence of contamination, yet finished product that was filled into bottles was adulterated with an unknown [redacted] containing contaminant. The product that was filled prior to the nasal spray was [redacted]. This episode raises concerns about the adequacy of your cleaning program. We strongly recommend that you evaluate your current policies for multi-use equipment and seriously consider whether pharmaceutical products should be manufactured in separate equipment.

Regarding the analytical issues identified for assay of [redacted] content of [redacted] the response letter fails to address the problems at hand. While Mr. Nash's letter describes procedures that will be established for all "*new*" methods, it makes no recommendation for resolving problems with the method currently used to release final product.

Regarding the question raised in the response letter about responsibility of contractors and their customers, you are reminded that ***all*** persons having authority and responsibility to prevent or correct violations of the Act are accountable and liable to do so. For your information we are forwarding a copy of this letter to [redacted] President and Chief Executive Officer of [redacted], to apprise him of our findings.

The cGMP deviations identified above are not an all-inclusive list of the deficiencies at your firm impacting on finished pharmaceuticals. FDA inspections are audits, and as such, are not intended to determine all deviations from cGMPs that exist at a firm. As top management, the responsibility to ensure that all requirements of the Act and its associated regulations are being met belongs to you.

You should take prompt action to correct the deviations identified above. Failure to take prompt corrective action may result in regulatory action without further notice. Possible actions include seizure and/or injunction. Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

Please respond to this letter within fifteen (15) days of receipt outlining the steps you have taken to correct cited deviations. Your reply should be directed to the attention of Ann L. deMarco, Compliance Officer, at the address noted on the letterhead.

Sincerely yours,

Thomas D. Gardine

Thomas D. Gardine
District Director
Philadelphia District